B3

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: 0 229 022 A2

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 87100615.1

(22) Date of filing: 21.07.83

(51) Int. Cl.⁴: A 61 K 31/52 //A61K45/06, (A61K31/52, 31:485)

(30) Priority: 22.07.82 US 400597
11.03.83 US 474358

(43) Date of publication of application: 15.07.87 Bulletin 87/29

(84) Designated Contracting States: AT BE CH DE FR GB LI LU NL SE

(60) Publication number of the earlier application in accordance with Art. 76 EPC: 0 114 888

(71) Applicant: SUNSHINE, Abraham
254 East 68 Street Apt. 12D
New York, NY 10021(US)

(71) Applicant: LASKA, Eugene M.
34 Dante Street
Larchmont, NY 10538(US)

(71) Applicant: SIEGEL, Carole E.
1304 Colonial Court
Mamaroneck, NY 10543(US)

(72) Inventor: SUNSHINE, Abraham
254 East 68 Street Apt. 12D
New York, NY 10021(US)

(72) Inventor: LASKA, Eugene M.
34 Dante Street
Larchmont, NY 10538(US)

(72) Inventor: SIEGEL, Carole E.
1304 Colonial Court
Mamaroneck, NY 10543(US)

(74) Representative: Kraus, Walter, Dr. et al,
Patentanwälte Kraus, Weisert & Partner
Thomas-Wimmer-Ring 15
D-8000 München 22(DE)

(54) **Novel pharmaceutical compositions comprising analgesic agents or caffeine.**

(57) Novel analgesic compositions for use in eliciting an analgesic response, said compositions comprising caffeine together with a selected non-narcotic analgesic/non-steroidal anti-inflammatory drug or a selected narcotic analgesic, or both, are disclosed. When used in combination with the selected drugs, caffeine enhances the analgesic response and also hastens its onset.

EP 0 229 022 A2

Croydon Printing Company Ltd.

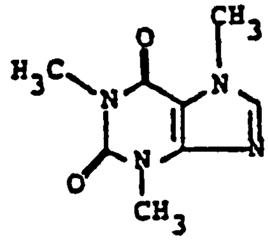
The present invention relates to novel pharmaceutical compositions comprising one or more analgesic agents or caffeine.

Non-narcotic analgesics, most of which are also known as non-steroidal anti-inflammatory drugs (NSAID), are widely administered orally in the treatment of mild to severe pain. Within this class, the compounds vary widely in their chemical structure and in their biological profiles as analgesics, anti-inflammatory agents and antipyretic agents. Aspirin®, acetaminophen and phenacetin have long been among the most commonly used members of this group; more recently, however, a large number of alternative non-narcotic agents

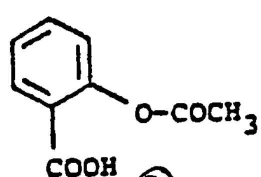
offering a variety of advantages over the earlier drugs have been developed. Tolerance or addiction to these drugs is not generally a problem with their continuous use in the treatment of pain or in the treatment of acute or chronic inflammatory states (notably, rheumatoid arthritis and osteoarthritis); nevertheless, these drugs generally have a higher potential for adverse side-effects at the upper limits of their effective dose ranges. Moreover, above each drug's upper limit or ceiling, administration of additional drug does not usually increase the analgesic or anti-inflammatory effect. Among the newer compounds in the non-narcotic analgesic/nonsteroidal anti-inflammatory group are compounds such as diflunisal (Dolobid®), ibuprofen (Motrin®), naproxen (Naprosyn®), fenoprofen (Nalfon®), piroxicam (Feldene®), flurbiprofen, mefenamic acid (Ponstel®) and sulindac. See also Physicians' Desk Reference, 35th edition, 1981, and The Merck Index, ninth edition, Merck & Co., Rahway, New Jersey (1976), for information on specific nonsteroidal anti-inflammatory agents. Also see, generally, Wiseman, "Pharmacological Studies with a New Class of Nonsteroidal Anti-Inflammatory Agents - The Oxicams - With Special Reference to Piroxicam (Feldene®), The American Journal of Medicine, February 16, 1982:2-8; Foley et al, The Management of Cancer Pain, Volume II - The Rational Use of Analgesics in the Management of Cancer Pain, Hoffman-LaRoche Inc., 1981; and Cutting's Handbook of Pharmacology, sixth edition, ed. T.Z. Czáky, M.D., Appleton-Century-Crofts, New York, 1979, Chapter 49: 538-550.

Narcotic analgesics are often used when pain control with non-narcotic analgesics is ineffective. While the drugs in this group vary considerably in their chemical structures and pharmacological properties, almost all suffer the disadvantages of tolerance and possible addiction with continued usage. Within the narcotic analgesic group, the drugs can be classified as narcotic agonists or narcotic antagonists. Narcotic agonists include the morphine group, the meperidine group and the methadone group. While some narcotic antagonists are pure antagonists (which are not analgesics), other narcotic antagonists are agonist-antagonists (i.e. antagonists with analgesic properties); the agonist-antagonists are generally categorized as morphine-like or nalorphine-like). Many of the narcotic analgesics are not effective orally, but are rather used parenterally. The orally active narcotic analgesics include such compounds as codeine, oxycodone, levorphanol (Levo-Dromoran®), meperidine (Demerol®), propoxyphene hydrochloride (Darvon®), propoxyphene napsylate (Darvon-N®), methadone, propiram, buprenorphine, pentazocine (Talwin®), nalbuphine (Nubain®) and butorphanol (Stadol®). For more specific information on these compounds, see Physicians' Desk Reference, 35th edition, 1981, and The Merck Index, ninth edition, Merck & Co., Inc., Rahway, New Jersey (1976). Also see, generally, the Foley et al reference cited hereinabove and Cutting's Handbook of Pharmacology, sixth edition, ed. T.Z. Czáky, M.D., Appleton-Century-Crofts, New York, 1979, Chapter 50: 551-566.

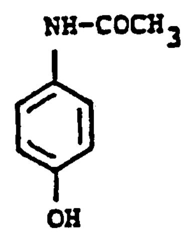
Caffeine, or 3,7-dihydro-1,3,7-trimethyl-1*H*-purine-2,6-dione, has the structural formula



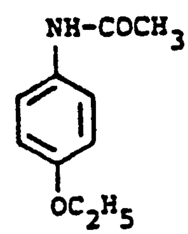
This substance has been used alone, intravenously, in the treatment of headaches and has also been used in combination with selected drugs. Compositions containing one or more of the analgesics Aspirin®, acetaminophen and phenacetin in combination with varying amounts of caffeine have been marketed in the past; in several cases, such non-narcotic analgesic/caffeine combination products have further included one of the narcotic analgesics codeine, propoxyphene or oxycodone. Examples of these combinations include the products known commercially as Excedrin®, SK-65® Compound, Darvon® Compound, Anacin®, A.P.C., and A.P.C. with Codeine, Tabloid® Brand. The nonsteroidal analgesic components of these mixtures have the following structural formulas:



Aspirin®
(acetylsalicyclic acid)

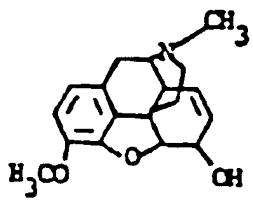


acetaminophen

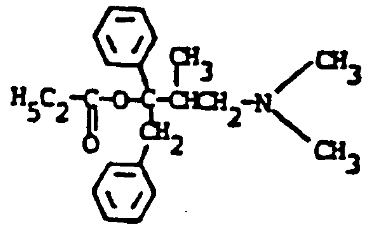


phenacetin

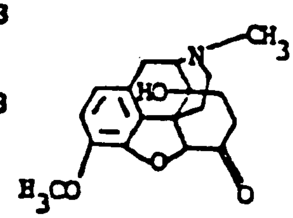
The three narcotic analgesics which have occasionally been added to the Aspirin®/phenacetin/acetaminophen/caffeine combinations have the following structural formulas:



codeine



propoxyphene



oxycodone

As far as the present inventors know, however, the art has never suggested that caffeine be added to a narcotic analgesic to contribute to <u>its</u> analgesic effect.

Many workers have sought to demonstrate the efficacy of the Aspirin®/phenacetin/acetaminophen/caffeine combination products. An extensive review of the literature on caffeine and analgesics has been published ["Over-The-Counter Drugs: Establishment of a Monograph for OTC Internal Analgesic, Antipyretic and Antirheumatic Products," <u>Federal Register</u>, 1977, <u>42</u> (131): 35482-35485] and several relevant additional articles have appeared. Most animal studies on caffeine analgesia have been performed on the rat. Williams (<u>Toxicology and Applied Pharmacology</u>, 1959, <u>1</u>:447-453) utilized experimental pain and found that caffeine alone exerted analgesic effects on rats and when combined with Aspirin® the effect appeared additive but not potentiating. Vinegar et al (<u>Proceedings of the Society for Experimental Biology and Medicine</u>, 1976, <u>151</u>:556-560), ten years later, found that in the rat caffeine potentiates the acute anti-inflammatory and analgesic activity of Aspirin®. Siegers (<u>Pharmacology</u>, 1973, <u>10</u>:19-27) studied the effect of oral doses of caffeine (10, 50 and 100 mg/kg) given to rats together with acetaminophen and found that caffeine inhibited its absorption and lowered its serum concentration. He

suggested that delayed stomach emptying as a result of the relaxing effect of caffeine on gastric smooth muscle was probably the cause of the diminished absorption of orally administered drugs in the presence of caffeine. Despite this finding, acetaminophen analgesia was not decreased by caffeine. In agreement with Williams and Vinegar and his associates, Siegers found that caffeine itself had analgesic activity. Only in the lowest dose of caffeine studied, a dose at which analgesia was not exhibited, was there a reduction in the acetaminophen induced analgesia. In a more recent paper, Seegers et al (Arch. Int. Pharmacodyn., 1981, 251:237-254) demonstrated an anti-inflammatory, analgesic effect of caffeine in rats. He also found that the combination of caffeine, aspirin and acetaminophen as well as the combination of caffeine, Aspirin® and phenacetin at low doses produced anti-inflammatory, analgesic effects which are at least as great as would be expected on the basis of addition, while at high doses, the results suggested potentiation. Citing the work of Giertz and Jurna (Naturwissenschaften, 1957, 44:445), and Fuchs and Giertz (Arzneimittelforsch, 1960, 10:526-530), who observed that caffeine induced analgesia in assays in mice in which inflammation was not involved, Seegers asserted that, "it seems safe to assume that the analgesic activity of caffeine consists of at least two components, one independent of and another one dependent on its anti-inflammatory activity."

The earliest relevant study in humans was reported by Wallenstein (Proceedings of the Aspirin® symposium, held at the Royal College of Surgeons, London, 1975). Two tablets of a combination in which each tablet

contained Aspirin® 210 mg, acetaminophen 150 mg and caffeine 30 mg, clearly and significantly produced more analgesia than the combination without caffeine. The one tablet dose of the combination had higher mean scores than either component alone, but was not superior to the combination without caffeine. Wallenstein speculated that, "dosage may be an important factor, and caffeine may simply be ineffective much below the 60 mg dose". Booy (Nederlands Tijdschrift Voor Tandheelkinde, 1972, 79:69-75) studied pain relief on each of two days after tooth extraction. Patients who reported "great pain" on the first day obtained more pain relief from 1000 mg of acetaminophen plus 100 mg of caffeine than from 1000 mg of acetaminophen alone. On the second day this difference was not found, although on both days all treatments were superior to placebo. Lim et al (Clin. Pharmacol. Ther., 1967, 8:521-542), reporting a study in which experimental pain was induced in the subjects by bradykinin, observed that the combination of Aspirin® 520 mg and acetaminophen 260 mg given orally could not be distinguished from placebo, whereas the same combination in lesser quantities, Aspirin® 325 mg and acetaminophen 162.5 mg plus caffeine 32.5 mg was significantly different from placebo at 15, 60, 75, 105, and 120 minutes after taking the drug. A double-blind, crossover study of 216 patients by Wojcicki et al [Archivum Immunologiae et Therapeae Experimentalis, 1977, 25(2):175-179] compared the activity of 1000 mg of acetaminophen plus 100 mg of caffeine against the same quantity of acetaminophen alone. One group of patients in the trial were suffering severe and frequently occurring idiopathic headache and a second group had

moderate post-operative orthopedic pain. The authors concluded that the relief of pain was far greater with the caffeine combination than with acetaminophen alone or with Aspirin alone. Jain et al (Clin. Pharmacol. Ther., 1978, 24:69-75) first studied 70 postpartum patients with moderate to severe uterine cramp and/or episiotomy pain and then a second group of 70 patients limited to severe pain only. Comparing 800 mg Aspirin plus 64 mg of caffeine to 650 mg Aspirin alone, these authors concluded that in patients with severe episiotomy pain the combination is the more effective analgesic.

Caffeine use in the treatment of headache has a long history. The FDA Advisory Panel, in its review of caffeine [Federal Register, 1977, 42 (131):35482-35485] argued that the known biochemical effect of caffeine on small blood vessels provides a plausible explanation for its effectiveness in treating headache associated with cerebral blood vessels. Recently Sechzer [Curr. Therapy Research, 1979, 26(4)] found that the intravenous administration of caffeine sodium benzoate rapidly provided relief in the majority of patients experiencing headache resulting from dural puncture or spinal anesthesia. The author, referring to the literature on the mechanism of action of caffeine on cerebral blood flow and on cerebral vascular tone, argues from the opposite perspective of the Panel that the analgesic relief obtained implies that an intracranial vascular component is the primary factor in such headaches.

Changes in mood and over-all sense of "well-being" after administration of caffeine have been widely reported in the literature. Beginning in the early part of this century, Hollingsworth (Arch. Psychol., 1912, 22:1) reported beneficial motor and mental effects from

65 to 130 mg of caffeine, and tremor, poor motor performance, and insomnia caused by 390 mg of caffeine. Many studies over the past 70 years have confirmed those findings. Review articles on the xanthines [Ritchie, J.M., "Central nervous system stimulants. 2. The xanthines," Goodman, L.S. & Gilman, A. (Eds.), The pharmacological basis of therapeutics, 4th Ed., New York: Macmillan Co., 1970; Stephenson, P.E., "Physiologic and psychotropic effects of caffeine on man," J. Amer. Diet. Assoc., 1977, 71(3):240-247] report that doses of 50 to 200 mg of caffeine result in increased alertness, decreased drowsiness, and lessened fatigue. Doses in the range of 200 to 500 mg may produce headaches, tremor, nervousness and irritability.

After extensively reviewing the relevant literature, the most significant contributions of which are summarized above, the FDA Advisory Panel in 1977 concluded that caffeine when used as an analgesic adjuvant was safe, but that there was insufficient data to demonstrate that caffeine contributes anything to the action of the analgesic [Federal Register, 1977, 42 (131): 35482-35485]. The Panel stated:

> Unfortunately, the information and data submitted, fail to demonstrate conclusively that caffeine in combination is effective as an analgesic, antipyretic and/or antirheumatic ingredient. The Panel finds there is little evidence to show that this ingredient even contributes to these pharmacological effects in the clinical situation.

This remains the official position on the question up to the present time. Consequently, many of the analgesic/caffeine combination products previously available are no longer on the market.

In addition to the few prior art instances of selected non-narcotic analgesic/caffeine combinations further containing a selected narcotic analgesic (which three-component combinations have already been discussed hereinabove), there also are examples in the art of two-component combinations of selected non-narcotic analgesics with selected narcotic analgesics. Known combinations of this type include Darvon® with A.S.A.® (propoxyphene hydrochloride and Aspirin®), Darvon-N® with A.S.A.® (propoxyphene napsylate and Aspirin®), Aspirin® with codeine, Talwin® Compound (pentazocine hydrochloride, oxycodone and aspirin), Percodan® (oxycodone hydrochloride, terephthalate and aspirin) and nalbuphine with acetaminophen, the last-mentioned combination being disclosed in U.S. Patent No. 4,237,140. The general principle of use of a combination of drugs to produce additive analgesic effects is known to those skilled in the art; for example, Foley et al, <u>The Management of Cancer Pain, Volume II - The Rational Use of Analgesics in the Management of Cancer Pain</u>, Hoffman-LaRoche Inc., 1981, suggest such combination and specifically point out that 650 mg Aspirin® or acetaminophen regularly added to the standard narcotic dose will often enhance the analgesic effect without requiring higher doses of the narcotic. Such additive effects have been reported earlier by Houde et al, <u>Clin. Pharm. Ther.</u> <u>1</u>(2):163-174(1960) for intramuscularly administered morphine sulfate given with orally administered Aspirin®. As far as the present inventors know, however, the art does not suggest any two-component compositions of a narcotic analgesic and caffeine; it also does not suggest any improvements in the analgesic response to be derived from co-administering caffeine with any narcotic analgesic.

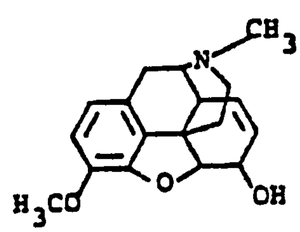
Surprisingly, the present inventors now find that orally effective narcotic analgesics (i.e. narcotic agonists and narcotic agonist-antagonists which are effective orally as analgesics) can likewise be advantageously formulated into novel pharmaceutical compositions together with caffeine and administered to mammals, especially humans, to not only elicit a more potent analgesic response but also to evoke such response more rapidly than possible by administration of the narcotic drug alone. The present inventors further find that orally effective narcotic analgesics can be advantageously combined with non-narcotic analgesics and caffeine to form novel pharmaceutical compositions which can be administered to mammals, especially humans, to elicit an improved analgesic response.

The present invention thus provides a novel pharmaceutical composition for use in eliciting an analgesic response, said composition comprising an effective analgesic amount of one or more of orally analgesically active narcotic agonist or agonist-antagonist and an amount of caffeine sufficient to hasten the onset of the analgesic response or to enhance the analgesic response.

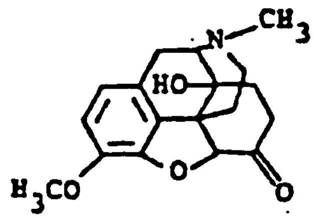
Typically, the active ingredients of the compositions of the invention are further associated with a nontoxic pharmaceutically acceptable inert carrier therefor.

The narcotic analgesics for use in the present invention are orally active narcotic agonists and narcotic agonist-antagonists (i.e. antagonists with analgesic properties). Suitable narcotic agonists for use herein include orally analgesically active members of the morphine group, the meperidine group and the methadone group, notably codeine, oxycodone, hydromorphone, levorphanol, meperidine, propoxyphene and methadone. Suitable agonist-antagonists for use herein include orally analgesically active antagonists of the morphine type, notably propiram and buprenorphine; and orally analgesically active antagonists of the nalorphine type, notably pentazocine, nalbuphine and butorphanol. Another suitable agonist-antagonist is meptazinol. In many instances, the narcotic analgesics for use herein are administered in the form of their pharmaceutically acceptable acid addition salts, e.g. codeine sulfate, codeine phosphate, oxycodone hydrochloride, oxycodone terephthalate, hydromorphone hydrochloride, levorphanol tartrate, meperidine hydrochloride, propoxyphene hydrochloride, propoxyphene napsylate, methadone hydrochloride, propiram fumarate, buprenorphine hydrochloride, nalbuphine hydrochloride and meptazinol hydrochloride. Structural formulas for representative free bases are shown below:

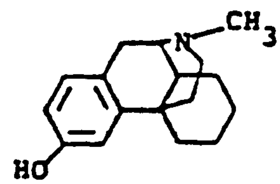
codeine



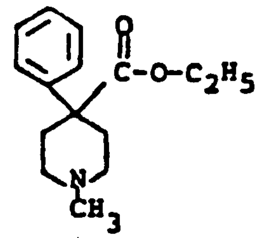
oxycodone



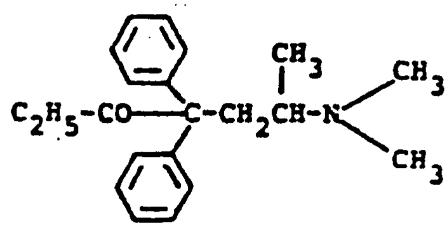
levorphanol



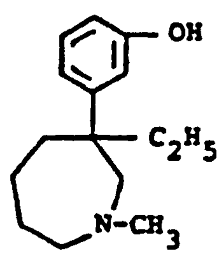
meperidine



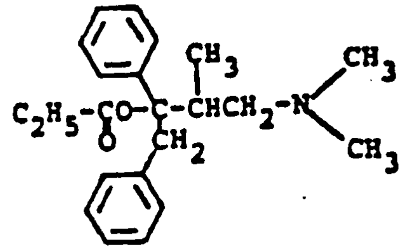
methadone



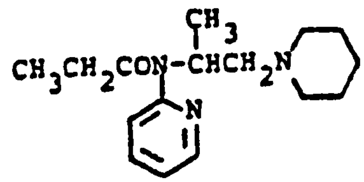
meptazinol



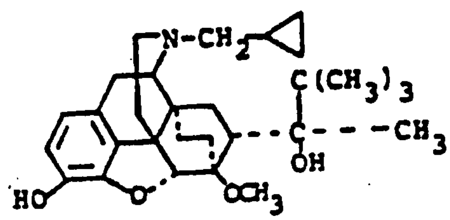
propoxyphene



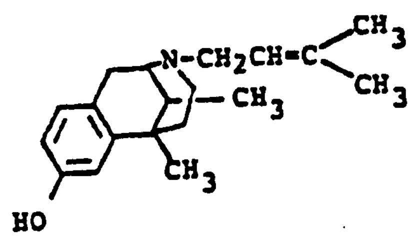
propiram



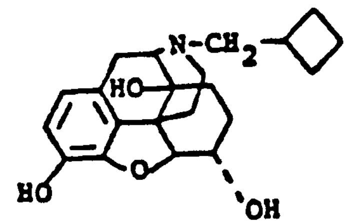
buprenorphine



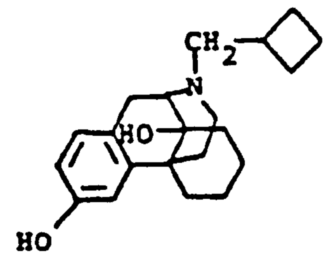
pentazocine



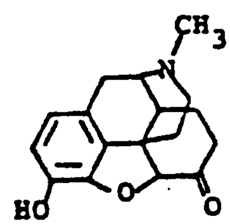
nalbuphine



butorphanol



hydromorphone



The term "caffeine" as used herein is intended to encompass not only caffeine as the anhydrous powder, but any salt or derivative of caffeine or any compounded mixture thereof which is non-toxic, pharmaceutically acceptable and which is capable of hastening and enhancing an analgesic or anti-inflammatory response when employed as described herein. See, for example, The Merck Index, ninth edition, Merck & Co., Inc. Rahway, New Jersey (1976), pp. 207-208, for a description of caffeine salts, derivatives and mixtures which may prove useful in the compositions of the present invention. Nevertheless, caffeine as the anhydrous powder base is presently preferred and, where specific amounts of caffeine are set forth below, such amounts are given in mg of the anhydrous base.

The term "selected narcotic analgesic" as used herein is intended to mean any orally analgesically active narcotic analgesic, be it an orally active narcotic agonist or a narcotic antagonist having oral analgesic activity. The term "selected narcotic analgesic" is used for the sake of simplicity in the discussion which follows.

The amount of caffeine in the analgesic composition will be an amount sufficient to shorten the onset time and/or to enhance analgesia. For humans, a unit dosage analgesic composition will typically contain from 60 to 200 mg (preferably 65 to 150 mg) caffeine; this dosage level of caffeine is generally sufficient to both shorten the onset time and enhance analgesia.

When a selected narcotic analgesic is combined with caffeine in accord with the present invention, the following unexpected results are produced:

(1) the analgesic effect of the selected narcotic analgesic is brought on more quickly;

(2) lower amounts of the selected narcotic analgesic are required for the same analgesic effect; and

(3) across all doses, a greater analgesic response is achieved.

For patients suffering pain, and most especially for patients suffering severe pain, the time from administration of medication to the onset of effective relief is clearly of paramount importance. The present inventors' discovery that caffeine substantially shortens the onset time, (i.e. substantially hastens the onset) of analgesia when it is combined with a selected narcotic analgesic is therefore highly significant; moreover, it is totally unexpected.

Further, the ability of caffeine to enhance analgesia, i.e. to substantially reduce the amount of selected narcotic analgesic which is required to elicit a given analgesic response, is also an unexpected and very important aspect of this invention. This unexpected

and important finding permits the use of the selected narcotic analgesic in quantities substantially less than the dosages presently suggested as an analgesic agent in humans. Use of lower doses should in turn lower the incidence and/or severity of undesirable side effects, including lessening addiction potential. Moreover, at a given dosage level, a greater analgesic response can be achieved.

More specifically, it is believed that onset time for analgesia can be reached, on the average, about one-fourth to about one-third sooner when a selected narcotic analgesic/caffeine composition of the invention is used rather than when the narcotic analgesic alone is employed. Also, approximately one-fifth to one-third less of the selected narcotic analgesic can be used in the caffeine combination to achieve the same analgesic effect as that obtained by use of the narcotic analgesic alone; in other words, the addition of caffeine decreases the amount of the selected narcotic analgesic to two-thirds to four-fifths of the usual amount to achieve the same effect. These ratios may vary, however, depending on the patient's individual response, the selected dosage level of the active ingredients etc.

The selected narcotic analgesic/caffeine compositions of the present invention are also advantageous in that the use of caffeine counteracts the sedative effects of the selected narcotic analgesic such that the patient is more alert, has better motor skills and may have an improved sense of well-being as compared to when the narcotic analgesic is administered alone.

The precise amount of selected narcotic analgesic for use in the present narcotic analgesic/caffeine compositions will vary depending, for example, on the specific drug chosen, the size and kind of the mammal and the condition for which the drug is administered. Generally speaking, the selected narcotic analgesic can be employed in any amount known to be an orally effective analgesic amount as well as at doses about one-fifth to one-third lower than the usual amounts.

For humans, typical effective analgesic amounts of presently preferred narcotics for use in unit dose narcotic analgesic/caffeine compositions of the present invention, to be administered every 4 to 6 hours as needed, are about 1 to 5 mg hydromorphone hydrochloride, about 15 to 60 mg codeine sulfate or phosphate, about 2.5 to 5 mg oxycodone hydrochloride or a mixture of oxycodone hydrochloride and oxycodone terephthalate (e.g. 4.50 mg oxycodone hydrochloride + 0.38 mg oxycodone terephthalate, or 2.25 mg oxycodone hydrochloride + 0.19 mg oxycodone terephthalate), about 1 to 3 mg levorphanol tartrate, about 50 mg meperidine hydrochloride, about 65 mg propoxyphene hydrochloride, about 100 mg propoxyphene napsylate, about 5 to 10 mg methadone hydrochloride, about 25 to 60 mg propiram fumarate, about 8 to 10 mg buprenorphine hydrochloride, about 25 to 50 mg pentazocine hydrochloride, about 10 to 30 mg nalbuphine hydrochloride, about 4 to 8 mg butorphanol tartrate or about 100 to 500 mg meptazinol hydrochloride. The amount of caffeine in the analgesic composition will be an amount sufficient to shorten the onset time and/or to enhance analgesia. For humans, a unit dosage analgesic composition will

typically contain from about 60 to about 200 mg (preferably about 65 to 150 mg) caffeine; this dosage level of caffeine is generally sufficient to both shorten the onset time and enhance analgesia. The daily analgesic dose in humans will vary with the selected narcotic analgesic, and may of course be as low as the amount contained in a single unit dose as set forth above. However, certain narcotic analgesics are particularly long-acting and need be administered less frequently than the usual every 4 to 6 hours. When such long-acting drugs are employed, it is often desirable to include an additional analgesia-enhancing amount of caffeine in the composition in sustained release form; thus, the composition will typically contain from 60 to 200 (preferably 65 to 150) mg caffeine for immediate release to hasten onset and enhance analgesia, and one (or possibly more) additional 60 to 200 (preferably 65 to 150) mg dose(s) of caffeine for sustained release to continue enhancement of analgesia. The daily analgesic dose in humans will vary with the selected narcotic analgesic and may of course be as low as the amount contained in a single unit dose as set forth above. The daily dose for use in the treatment of moderate to severe pain will preferably not exceed 30 mg hydromorphone hydrochloride, or 360 mg codeine sulfate or phosphate, or 60 mg oxycodone hydrochloride or hydrochloride/terephthalate mixture, or 18 mg levorphanol tartrate, or 600 mg meperidine hydrochloride, or 390 mg propoxyphene hydrochloride, or 600 mg propoxyphene napsylate, or 60 mg methadone hydrochloride, or 300 mg propiram fumarate, or 60 mg buprenorphine hydrochloride, or 300 mg pentazocine hydrochloride, or 180 mg nalbuphine hydrochloride, or 48 mg butorphanol tartrate, or 3000 mg meptazinol hydrochloride, and 1000 mg caffeine, although greater amounts could be employed if tolerated by the patient.

While the compositions of the invention are preferably for oral use, they may also be formulated for and administered by other methods which are known for administering analgesics, e.g. as suppositories. Also, the preferred human dosage levels indicated above are for use in adults; pediatric compositions would contain proportionately less of the active ingredients.

The compositions of the present invention are very conveniently administered to mammals by any route of administration suitable for the selected narcotic analgesic component, e.g. oral or rectal. Preferably, the combination is formulated with any suitable nontoxic pharmaceutically acceptable inert carrier material. Such carrier materials are well known to those skilled in the art of pharmaceutical formulations. For those not skilled in the art, reference is made to the text entitled "REMINGTON'S PHARMACEUTICAL SCIENCES" (Fourteenth Edition), 1970. In a typical preparation for oral administration, e.g., tablet or capsule, the selected narcotic analgesic in an effective analgesic amount and caffeine in an amount sufficient to enhance the analgesic response or to hasten its onset, are combined with any oral nontoxic pharmaceutically acceptable inert carrier such as lactose, starch (pharmaceutical grade), dicalcium phosphate, calcium sulfate, kaolin, mannitol and powdered sugar. Additionally, when required, suitable binders, lubricants, disintegrating agents and coloring agents can also be included. Typical binders include starch, gelatin, sugars such as sucrose, molasses and lactose, natural and synthetic gums such as acacia,

sodium alginate, extract of Irish moss, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone, polyethylene glycol, ethylcellulose and waxes. Typical lubricants for use in these dosage forms can include, without limitation, boric acid, sodium benzoate, sodium acetate, sodium chloride, leucine and polyethylene glycol. Suitable disintegrators can include, without limitation, starch, methylcellulose, agar, bentonite, cellulose, wood products, alginic acid, guar gum, citris pulp, carboxymethylcellulose and sodium lauryl sulfate. If desired, a conventional pharmaceutically acceptable dye can be incorporated into the dosage unit form, i.e., any of the standard FD&C dyes. Sweetening and flavoring agents and preservatives can also be included, particularly when a liquid dosage form is formulated, e.g. an elixir, suspension or syrup. Also, when the dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. Such compositions should preferably contain at least 0.1% of active components; generally, the active ingredients will be between about 2% to about 60% of the weight of the unit.

Illustrative of typical unit dosage forms are tablets or capsules containing the amounts indicated in the table below. Note that the asterisk (*) indicates that the adjacent amount is in sustained release form, e.g. "130 mg + 130 mg*" means that the first 130 mg is formulated for immediate release, while the second 130 mg is in sustained release form.

TABLE

Selected Narcotic Analgesic	Caffeine
hydromorphone hydrochloride,	
1 mg	130 mg
2 mg	130 mg
3 mg	130 mg
4 mg	130 mg
5 mg	130 mg
codeine sulfate or phosphate,	
15 mg	130 mg
30 mg	130 mg
45 mg	130 mg
60 mg	130 mg
oxycodone hydrochloride,	
2.5 mg	130 mg
5 mg	130 mg
meptazinol hydrochloride,	
200 mg	65 or 130 mg

TABLE con't

Selected Narcotic Analcesic	Caffeine
oxycodone hydrochloride/ terephthalate mixture,	
4.5 mg/0.38 mg	130 mg
2.25 mg/0.19 mg	130 mg
levorphanol tartrate,	
1 mg	130 mg
2 mg	130 mg
3 mg	130 mg
meperidine hydrochloride, 50 mg	130 mg
propoxyphene hydrochloride, 65 mg	130 mg
propoxyphene napsylate, 100 mg	130 mg
methadone hydrochloride,	
5 mg	130 mg
10 mg	130 mg
propiram fumarate,	
35 mg	65 or 130 mg
50 mg	130 mg
buprenorphine hydrochloride,	
8 mg	130 mg
10 mg	130 mg
pentazocine hydrochloride,	
25 mg	65 or 130 mg
50 mg	130 mg
nalbuphine hydrochloride,	
10 mg	130 mg
15 mg	65 or 130 mg
30 mg	130 mg

TABLE con't

Selected Narcotic Analcesic	Caffeine
butorphanol tartrate,	
4 mg	130 mg
8 mg	65 or 130 mg

If desired, compositions of the present invention may be formulated for parenteral use by known methods. The two-component selected narcotic analgesic/caffeine composition is of particular value in the case of patients suffering severe pain who cannot tolerate such medication administered orally.

It is also possible to formulate the oral compositions of the invention in such a manner that the possibility that the narcotic analgesic could be extracted therefrom and then abused parenterally will be significantly reduced. This may be accomplished by combining the drugs with insoluble excipients such as methylcellulose to form a dosage form that is insoluble in water. Such water-insoluble oral dosage forms are already known for at least some of the narcotics themselves, e.g. for propiram fumarate and methadone hydrochloride.

The analgesic and anti-inflammatory effects of the compositions of the present invention can be quantitatively evaluated in animals in the tests described below:

<u>Antiphenylquinone Writhing Test</u>:

This test is a standard procedure for detecting and comparing analgesic activity and generally correlates well with human efficacy.

Mice are first dosed with the medications studied. The medications used are two dose levels of a selected narcotic analgesic with and without caffeine. The mice are then challenged with phenyl-p-benzoquinone given intraperitoneally and observed for the characteristic stretch-writhing syndrome.

Lack of writhing constitutes a positive response. The degree of analgesic protection can be calculated on the basis of suppression of writhing relative to control animals run the same day. Time response data are also obtained. The test is a modification from the methods of Sigmund et al and Blumberg et al (Sigmund, E., Cadmus, R., and Lu, G., Proc. Soc. Exp. Biol. and Med. 95, 729-731, 1957; Blumberg, H. et al, Proc. Soc. Exp. Biol. Med. 118, 763-766, 1965).

The Inflamed Rat Paw Test: - Pressure Induced Stimuli.

The method of Randall-Selitto, modified according to Winter et al is used to ascertain the escape response threshold resulting from the application of increasing pressure to the yeast inflamed left hind paw. Drug treatment is given. The medications studied are two dose levels of a selected NSAID with and without caffeine. A constantly increasing force is applied to the paw and the "flight reaction" is observed and recorded (Randall, L.Q., and Selitto, J.J.: Arch. Int. Pharmacodyn., II, 409-419, 1957; Winter, C.A., and Lars, F.: J. Pharmacol. Exp. Therap., 148, 373-379, 1965).

The Mouse Tail-flick Test:

Tail-flick testing in mice is modified after D'Amour and Smith, using controlled high intensity heat applied to the tail. Normal and drug-treated mice are observed and the reaction time is measured. The drugs used are two doses of a selected narcotic analgesic with and without caffeine. (D'Amour, E., and Smith, L., J. Pharmacol., 72, 74-79, 1941).

Haffner Tail-Pinch Method:

A modification of the procedure of Haffner is used to ascertain drug effects on the aggressive attacking responses elicited by a pressure stimulus pinching the

tail of a rat. A clamp is on the base of each rat's tail prior to drug treatment and again at specified intervals after treatment. The time required to elicit clear attacking and biting behavior directed towards the stimulus is observed. The medications studied are two doses of a selected narcotic analgesic with and without caffeine. (Haffner, F.: Experimentelle Prüfung Schmerzstillender Mittel. Deutsch med. Wschr., 55, 731-732, 1929).

Mouse Hot-Plate Test (Thermal Stimuli):

A modification of the method of Woolfe and MacDonald is used and involves the application of a controlled heat stimulus to the paws of mice. Drug is administered to the treatment group. The latency between the time of the animal's contact with the hot-plate and the observation of the standard pain response, jumping and/or rapid patting of one or both hind paws is measured. The medications studied are two doses of a selected narcotic analgesic with and without caffeine. (Woolfe, G., and MacDonald, A.D.: J. Pharmacol. Exp. Ther., 80, 300-307, 1944).

Adjuvant Arthritis Test:

Adjuvant arthritis in the rat is a widely used model for human rheumatoid arthritis. It is basically an immunological reaction, involving a cellular immune response to an injected bacterial adjuvant. The response is systemic, but develops mainly in the limbs as a polyarthritis. The degree of arthritis in the hind legs is assessed either visually or by measuring the foot volume on the 21st day after injection of the adjuvant.

A single subcutaneous injection of 1 mg *Mycobacterium butyricum* suspended in 0.1 ml mineral oil is injected into the right hindpaws of rats. The

swelling of the injected hind leg measured on day 16 constitutes the secondary response. Drugs are administered p.o. daily, beginning 1 day prior to injection of adjuvant. The medications used are two dose levels of selected NSAID with and without caffeine. Results are expressed as percent suppression of the control. [Walz, D.T., Di Martino, M.J., and Misher, A.: Ann. Rheum. Dis., 30, 303-306 (1971)].

To establish the efficacy of the compositions of this invention in humans, patients with moderate to severe pain requiring an oral analgesic can be administered a selected narcotic analgesic with and without caffeine or a selected narcotic analgesic. To determine analgesic efficacy, a nurse observer interviews the patients as to their level of pain at subsequent periods of time. Patients are asked to subjectively estimate the time at which the medication begins to provide relief. Appropriate statistical methods can be used to show that on the average the compositions with caffeine have shorter onset and are more efficacious. (Laska, E., Gormely, M., Sunshine, A., Belleville, J.W., Kantor, T., Forrest, W.H., Siegel, C., and Meisner, M.: "A Bioassay Computer Program for Analgesic Clinical Trials", Clin. Pharmacol. Ther. 8: 658, 1967; Cox, D.R., "Regression Models and Life Tables", Journal Royal Statistical Society, Series B, Volume 34: 187-202, 1972).

C L A I M S for the Contracting States

BE, CH, DE, FR, GB, LI, LU, NL and SE

1. A pharmaceutical composition adapted to elicit an onset hastened and enhanced analgesic response in a mammalian organism in need of such treatment, said composition consisting of a unit dosage analgesically effective amount of (i) an orally analgesically active narcotic analgesic, (ii) a narcotic analgesic potentiating adjuvant therefor, said adjuvant consisting of a narcotic analgesic onset hastening and enhancing amount of caffeine, and (iii) a nontoxic pharmaceutically acceptable inert carrier.

2. The pharmaceutical composition as defined by Claim 1, said orally analgesically active narcotic analgesic comprising a narcotic agonist.

3. The pharmaceutical composition as defined by Claim 1, said orally analgesically active narcotic analgesic comprising a narcotic antagonist.

4. A pharmaceutical composition adapted to elicit an onset hastened and enhanced analgesic response in a mammalian organism in need of such treatment, said composition comprising a unit dosage analgesically effective amount of an orally analgesically active narcotic antagonist and a narcotic antagonist potentiating adjuvant therefor, said adjuvant consisting of a narcotic antagonist onset hastening and enhancing amount of caffeine.

5. The pharmaceutical composition as defined by Claim 1, said narcotic analgesic comprising pentazocine hydrochloride, nalbuphine hydrochloride, butorphenol tartrate or meptazinol hydrochloride.

6. The pharmaceutical composition as defined by Claim 1, said narcotic analgesic comprising propoxyphene hydrochloride, propoxyphene napsylate, codeine sulfate or codeine phosphate.

CLAIMS for the Contracting State AT

1. A pharmaceutical composition adapted to elicit an onset hastened and enhanced analgesic response in a mammalian organism in need of such treatment, said composition consisting of a unit dosage analgesically effective amount of (i) an orally analgesically active narcotic analgesic, (ii) a narcotic analgesic potentiating adjuvant therefor, said adjuvant consisting of a narcotic analgesic onset hastening and enhancing amount of caffeine, and (iii) a nontoxic pharmaceutically acceptable inert carrier.

2. The pharmaceutical composition as defined by Claim 1, said orally analgesically active narcotic analgesic comprising a narcotic agonist.

3. The pharmaceutical composition as defined by Claim 1, said orally analgesically active narcotic analgesic comprising a narcotic antagonist.

4. A pharmaceutical composition adapted to elicit an onset hastened and enhanced analgesic response in a mammalian organism in need of such treatment, said composition comprising a unit dosage analgesically effective amount of an orally analgesically active narcotic antagonist and a narcotic antagonist potentiating adjuvant therefor, said adjuvant consisting of a narcotic antagonist onset hastening and enhancing amount of caffeine.

5. The pharmaceutical composition as defined by Claim 1, said narcotic analgesic comprising pentazocine hydrochloride, nalbuphine hydrochloride, butorphenol tartrate or meptazinol hydrochloride.

6. The pharmaceutical composition as defined by Claim 1, said narcotic analgesic comprising propoxyphene hydrochloride, propoxyphene napsylate, codeine sulfate or codeine phosphate.

7. A process for the production of a pharmaceutical composition adapted to elicit an onset hastened and enhanced analgesic response in a mammalian organism in need of such treatment, comprising combining a unit dosage analgesically effective amount of (i) an orally analgesically active narcotic analgesic, (ii) a narcotic analgesic potentiating adjuvant therefor, said adjuvant consisting of a narcotic analgesic onset hastening and enhancing amount of caffeine, and (iii) a nontoxic pharmaceutically acceptable inert carrier.

8. The process of Claim 7, said orally analgesically active narcotic analgesic comprising a narcotic agonist.

9. The process of Claim 7, said orally analgesically active narcotic analgesic comprising a narcotic antagonist.

10. The process of Claim 7 for the production of a pharmaceutical composition in which said narcotic analgesic comprises pentazocine hydrochloride, nalbuphine hydrochloride, butorphenol tartrate or meptazinol hydrochloride.

11. The process of Claim 7 for the production of a pharmaceutical composition in which said narcotic analgesic comprises propoxyphene hydrochloride, propoxyphene napsylate, codeine sulfate or codeine phosphate.

12. A process for the production of a pharmaceutical composition adapted to elicit an onset hastening and

enhanced analgesic response in a mammalian organism in need of such treatment, comprising combining a unit dosage analgesically effective amount of an orally analgesically active narcotic antagonist and a narcotic antagonist potentiating adjuvant therefor, said adjuvant consisting of a narcotic antagonist onset hastening and enhancing amount of caffeine.